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TITLE: PRO 2000 Gel, A Candidate Topical Microbicide, Can Inhibit Vaginal Simian/Human Immunodeficiency Virus Infection in Rhesus Macaques

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BACKGROUND/OBJECTIVES: PRO 2000 Gel is a candidate topical microbicide designed to prevent the sexual transmission of HIV and other STD pathogens. Laboratory studies have shown that the naphthalene sulfonate polymer PRO 2000 is active in vitro against HIV-1, HIV-2, herpes simplex viruses (HSV-1 and HSV-2), human cytomegalovirus, Chlamydia trachomatis and Neisseria gonorrhoeae. Moreover, intravaginally applied PRO 2000 Gel was shown to prevent intravaginal HSV-2 infection in mice, and to inhibit conception in artificially inseminated rabbits. Nonclinical toxicology studies and Phase I clinical trials in healthy, sexually abstinent women indicated that gels containing UP to 4% PRO 2000 are safer than marketed spermicides containing the detergent nonoxynol-9 (N-9). The goal of the present work was to evaluate the protective efficacy of PRO 2000 Gel in a nonhuman primate model for vaginal HIV-1 transmission. A chimeric simian/human immunodeficiency virus (SHIV) expressing the HIV-I env gene was used because the mechanism of action of PRO 2000 is believed to involve the envelope glycoprotein.

METHODS: Female rhesus' macaques (4 per group) were treated with an intravaginal dose of test agent (1 mL) followed, 15 min later, by intravaginal placement of a titered SHIV-89.6PD stock (1.7 mL, kindly provided by Y. Lu, Virus Research Institute). A second identical cycle of gel application and viral challenge was performed 3 h after the first challenge. Over the following 12 weeks, animals were periodically tested for isolatable virus (by PBMC coculture) and plasma SHIV RNA (by the bDNA assay). For animals that remained coculture negative, attempts were made to isolate virus from lymph node tissue collected at autopsy. Test agents included 2% and 4% PRO 2000 Gel and a marketed 4% N-9 gel. Control animals were not treated before challenge.

RESULTS: The infection status of each animal was unambiguous. The proportion of animals infected in each group was as follows: Controls (3/4); 4% N-9 gel (1/4); 2% PRO 2000 Gel (3/4); 4% PRO 2000 Gel (1/4).

DISCUSSION: The results provide the first evidence that PRO 2000 Gel can inhibit vaginal lentivirus infection in primates. Though the relevance of the macaque model to the human situation is unknown, the high rate of infection in the untreated control group suggests that it is a stringent test. It is encouraging that the number of uninfected animals in the 4% PRO 2000 Gel group was the same as in the N-9 group, since 4% N-9 is potentially virucidal. In the macaque model, the effectiveness of N-9 should not have been compromised by epithelial disruption, which is known to occur upon frequent N-9 use in humans. Based on the results, additional studies of PRO 2000 Gel are warranted.

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